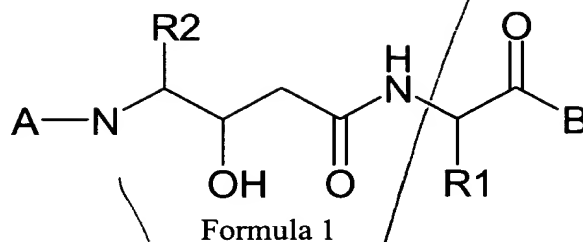


Claims

We claim:

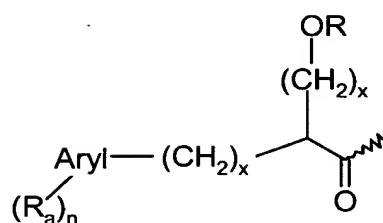
1) A compound of formula 1



wherein:

A is

i)

*Hydrogen*

wherein Aryl is mono or bicyclic and has from 5 to 10 ring atoms and may optionally include up to 3 heteroatoms chosen from N, O and S;

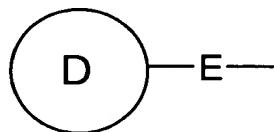
each x is independently 0, 1 or 2;

R is H, C<sub>1</sub>-C<sub>6</sub> alkyl, phenyl or benzyl wherein each phenyl ring is optionally substituted with up to two groups independently selected from -OH; -CH<sub>2</sub>OH, -CO<sub>2</sub>H, -CF<sub>3</sub>, Cl, Br, F; and C<sub>1</sub>-C<sub>2</sub> alkyl;

each R<sub>a</sub> is independently selected from the group consisting of H, OH, C<sub>1</sub>-C<sub>3</sub> alkyl; C<sub>1</sub>-C<sub>6</sub> alkylacylamino, C<sub>1</sub>-C<sub>6</sub> alkylacyloxy, C<sub>1</sub>-C<sub>6</sub> alkyloxy, C<sub>1</sub>-C<sub>6</sub> alkylthioxy, amido (including primary, C<sub>1</sub>-C<sub>6</sub> alkyl and phenyl secondary and tertiary), NH<sub>2</sub>, mono and di(C<sub>1</sub>-C<sub>6</sub> alkyl and phenyl) amino, carbamyl (including C<sub>1</sub>-C<sub>6</sub> alkyl and phenyl amides and esters), carboxyl (including C<sub>1</sub>-C<sub>6</sub> alkyl and phenyl esters), carboxy(C<sub>2</sub>-C<sub>5</sub>)alkyloxy and N-heterocyclacyl;

and n is 1 or 2;

ii)



wherein D is chosen from aryl having 5 to 6 atoms, optionally including up to 2 heteroatoms selected from the N, O, and S; fused aryl

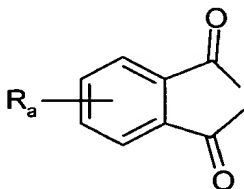
of 8 to 14 atoms optionally including up to 3 heteroatoms selected from the N, O, and S; mono or fused cycloalkyl having 5 to 12 carbon atoms; and mono or fused heterocycloalkyl having 5 to 12 carbon atoms including up to 3 heteroatoms selected from N, O, and S; biaryl, diaryl ether; diarylketone, and phenyl(C<sub>1</sub>-C<sub>8</sub>) alkyloxyaryl;

and wherein E is a divalent group chosen from carbonyl, sulfonyl, C<sub>1</sub>-C<sub>3</sub> alkylene, -X- (C<sub>1</sub>-C<sub>3</sub>) alkylcarbonyl wherein X is chosen from N, O and S, or E is merely a bond;

and D may optionally be substituted with up to two groups chosen from OH, C<sub>1</sub>-C<sub>3</sub> alkyl; C<sub>1</sub>-C<sub>6</sub> alkylacylamino, C<sub>1</sub>-C<sub>6</sub> alkylacyloxy, C<sub>1</sub>-C<sub>6</sub> alkyloxy, C<sub>1</sub>-C<sub>6</sub> alkylthioxy, amido (including primary, C<sub>1</sub>-C<sub>6</sub> alkyl and phenyl secondary and tertiary), NH<sub>2</sub>, mono and di(C<sub>1</sub>-C<sub>6</sub> alkyl and phenyl) amino, carbamyl (including C<sub>1</sub>-C<sub>6</sub> alkyl and phenyl amides and esters), carboxyl (including C<sub>1</sub>-C<sub>6</sub> alkyl and phenyl esters), carboxy(C<sub>2</sub>-C<sub>5</sub>)alkyloxy, N-heterocyclacyl, C<sub>1</sub>-C<sub>3</sub> alkylsulfonyl, sulfonamide and C<sub>1</sub>-C<sub>3</sub> alkylsulfonamide;

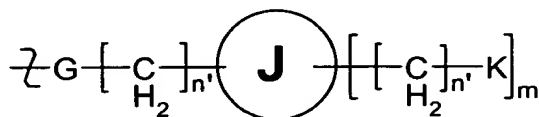
iii) C<sub>1</sub>-C<sub>6</sub> alkanoyl; C<sub>2</sub>-C<sub>6</sub> alkenoyl; and methylthioC<sub>1</sub>-C<sub>5</sub> alkanoyl, any of which may be substituted with up to two groups chosen from OH, C<sub>1</sub>-C<sub>6</sub> alkylacylamino, C<sub>1</sub>-C<sub>6</sub> alkylacyloxy; C<sub>1</sub>-C<sub>6</sub> alkyloxy; C<sub>1</sub>-C<sub>6</sub> alkylthioxy, amido (including primary, C<sub>1</sub>-C<sub>6</sub> alkyl secondary; C<sub>1</sub>-C<sub>6</sub> alkyl and phenyl tertiary, amino, C<sub>1</sub>-C<sub>6</sub> alkyl and phenyl amino, carbamyl (including C<sub>1</sub>-C<sub>6</sub> alkyl and phenyl amides and esters), carboxyl (including C<sub>1</sub>-C<sub>6</sub> alkyl and phenyl esters), carboxy(C<sub>2</sub>-C<sub>5</sub>)alkyloxy and N-heterocyclacyl, C<sub>1</sub>-C<sub>3</sub> alkylsulfonyl, sulfonamide and C<sub>1</sub>-C<sub>3</sub> alkylsulfonamide;

and iv) a divalent group of the formula:



wherein each carbonyl of the divalent group bonds to the nitrogen to form a five membered ring and R<sub>a</sub> is as defined above;

B is selected from -OH; C<sub>1</sub>-C<sub>6</sub> alkyl or C<sub>1</sub>-C<sub>6</sub> alkyl amino, di(C<sub>1</sub>-C<sub>6</sub> alkyl)amino, C<sub>1</sub>-C<sub>6</sub> alkyloxy, N-heterocyclic and



each  $n'$  is independently 0, 1 or 2;

$m$  is 0, 1, 2 or 3;

5 and  $G$  is N or O;

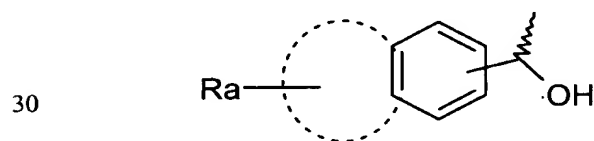
$J$  is selected from the group consisting of aryl having a 5 to 6 membered ring optionally including up to 2 heteroatoms selected from the N, O, and S; fused aryl rings of 8 to 14 atoms optionally including up to 3 heteroatoms selected from N, O, and S, mono or fused ring cycloalkyl having 5 to 12 carbon atoms; and mono or fused ring heterocyclic having  
10 5 to 12 carbon atoms including up to 3 heteroatoms chosen from the group consisting of N, O, and S;

each  $K$  is chosen from OH,  $C_1$ - $C_3$  alkyl;  $C_1$ - $C_6$  alkylacylamino,  $C_1$ - $C_6$  alkylacyloxy,  $C_1$ - $C_6$  alkyloxy,  $C_1$ - $C_6$  alkylthioxy, amido (including primary,  $C_1$ - $C_6$  alkyl and phenyl secondary  
15 and tertiary),  $NH_2$ , mono and di( $C_1$ - $C_6$  alkyl and phenyl) amino, carbamyl (including  $C_1$ - $C_6$  alkyl and phenyl amides and esters), carboxyl (including  $C_1$ - $C_6$  alkyl and phenyl esters) and carboxy( $C_2$ - $C_5$ )alkyloxy;

$R_1$  is straight or branched chain  $C_1$ - $C_5$  alkanyl or  $C_2$ - $C_5$  alkenyl;

20  $R_2$  is  $C_{1-5}$  straight or branched chain alkanyl or alkenyl; methylthiomethyl; aryl or arylalkyl or heteroaryl or heteroarylalkyl wherein any of the above are optionally substituted with up to 2 of  $C_{1-3}$  alkyl, trifluoromethyl or halogen, and stereoisomers, hydrates or pharmaceutically acceptable salts thereof.

25 2) The compound claim 1 wherein A is:

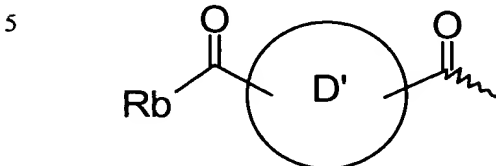


wherein the dotted line indicates an optional aryl ring fused to the phenyl ring.

35 3) The compound of claim 2 wherein the A is selected from 2-hydroxy-(2-phenyl)ethanoyl, 2-hydroxy-(2-naphth-1-yl)ethanoyl, and 2-hydroxy-(2-naphth-12-yl)ethanoyl.

4) The compound of claim 1 wherein A is selected from biphenyl, 2-phenyl- $\alpha$ -hydroxytolyl, diphenyl ether and diphenyl ketone.

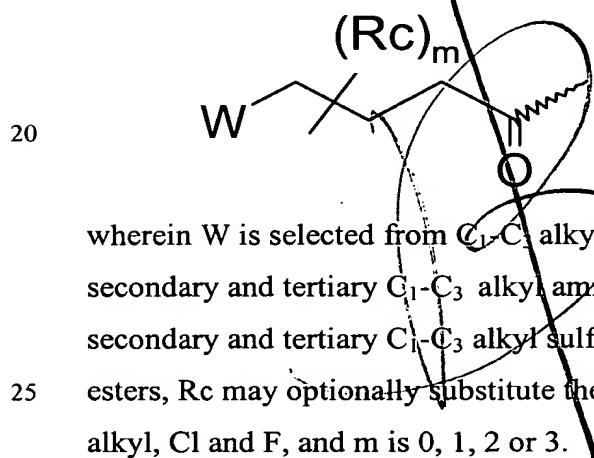
5) The compound of claim 1 wherein A is



10 wherein the ring D' is a 5 or 6 membered monocyclic aryl or heteroaryl ring including up to 3 atoms selected from N, O and S, and Rb is  $\text{-NH}_2$ , mono and di( $\text{C}_1\text{-C}_6$  alkyl) amino,  $\text{C}_1\text{-C}_6$  alkoxy, N-heterocyclic and  $\text{C}_1\text{-C}_6$  alkyl.

6) The compound of claim 5 wherein the ring D' is chosen from the group consisting of benzene, pyridine, furan, thiophene, thiazole, thiadiazole, oxazole, oxadiazole and 1,2,4-triazole and Rb is di( $\text{C}_2\text{-C}_4$ )alkylamine.

7) The compound of claim 1 wherein A is



8) The compound of claim 1 wherein R1 is selected from ethyl and 2-propyl.

30 9) The compound of claim 1 wherein R2 is selected from 2-thienylmethyl, 3-trifluoromethylphenylmethyl, 4-thiazolylmethyl, 3-chlorophenylmethyl, 3,5-difluorophenylmethyl, 4-methylphenylmethyl and 2-methylprop-1-yl.

10) The compound of claim 1 wherein R1 is 2-propyl and R2 is 3,5-difluorophenylmethyl.

35

11) The compound of claim 3 wherein R1 is 2-propyl and R2 is 3,5-difluorophenyl-methyl.

5 12) The compound of claim 5 wherein R1 is 2-propyl and R2 is 3,5-difluorophenyl-methyl.

13) The compound of claim 7 wherein R1 is 2-propyl and R2 is 3,5-difluorophenyl-methyl.

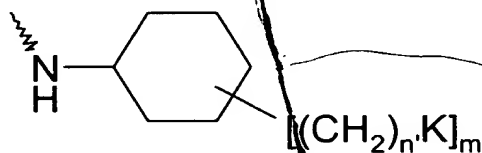
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14) The compound of claim 1 wherein B is -OH, C<sub>1</sub>-C<sub>6</sub> alkoxy, mono and di(C<sub>1</sub>-C<sub>6</sub>) alkylamino, aminoC<sub>1</sub>-C<sub>4</sub> alkyl-p-benzoic acid and C<sub>1</sub>-C<sub>6</sub> alkyl and phenyl esters thereof and N-heterocyclic.

15

15) The compound of claim 1 wherein B is

B is



"j" must be aryl, not cycloalkyl

20

wherein K, n' and m are as defined in claim 1.

16) The compound of claim 15 wherein B is selected from 3,5-dicarboxycyclohexylamine, 3,4- dicarboxycyclohexylamine, 3,5- dimethoxycyclohexylamine, 3,5-dihydroxymethylcyclohexylamine and 3,4,5-trimethoxycyclohexylamine.

25

17) The compound of claim 1 wherein A is selected according to claim 2 and B is selected according to claim 14.

30

18) The compound of claim 1 wherein A is selected according to claim 2 and B is selected according to claim 15.

19) The compound of claim 1 wherein A is selected according to claim 5 and B is selected according to claim 14.

20) The compound of claim 1 wherein A is selected according to claim 15 and B is selected according to claim 15.

21) The compound of claim 1 wherein A is selected according to claim 7 and B is selected according to claim 14.

22) The compound of claim 1 wherein A is selected according to claim 7 and B is selected according to claim 15.

23) A compound selected from the group consisting of:

10 *N*-{*N'*-[2-hydroxy-2-(naphth-1-yl)ethanoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-6-methylheptanoyl} valine (4-carboxy)phenylmethanamide

*N*-{*N'*-[2-hydroxy-2-(naphth-1-yl)ethanoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-6-methylheptanoyl} valine 2-[(4-carboxy)phenyl]ethanamide

15 *N*-{*N'*-[2-hydroxy-2-(naphth-1-yl)ethanoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-6-methylheptanoyl} valine 3-carboxypropylamide

20 *N*-{*N'*-[2-hydroxy-2-(naphth-1-yl)ethanoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-6-methylheptanoyl} valine 4-carboxynaphth-1-ylmethanamide

*N*-{*N'*-[2-hydroxy-2-(naphth-1-yl)ethanoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-6-methylheptanoyl} valine *cis*, *cis*-3,5-dicarboxycyclohexylamide

25 *N*-{*N'*-[2-hydroxy-2-(naphth-1-yl)ethanoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-6-methylheptanoyl} valine 4-carboxycyclohexylamide

*N*-{*N'*-[2-hydroxy-2-(naphth-1-yl)ethanoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-6-methylheptanoyl} valine

30 *N*-{*N'*-[2-benzyloxy-2-(naphth-1-yl)ethanoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-6-methylheptanoyl} valine (4-carboxy)phenylmethanamide

35 *N*-[*N'*-(3-hydroxy-2-phenylpropanoyl)-(3*S*, 4*S*)-4-amino-3-hydroxy-6-methylheptanoyl] valine (4-carboxy)phenylmethanamide

*N*-{*N'*-[2-hydroxy-2-(2-bromophenyl)ethanoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-6-methylheptanoyl} valine (4-carboxy)phenylmethanamide

40 *N*-{*N'*-[(*S*)-2-hydroxy-3-phenylpropanoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-6-methylheptanoyl} valine (4-carboxy)phenylmethanamide

*N*-{*N'*-[2-hydroxy-2-(3-phenoxyphenyl)ethanoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-6-methylheptanoyl} valine (4-carboxy)phenylmethanamide

45 *N*-{*N'*-[(*R*)-2-hydroxy-3-phenylpropanoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-6-methylheptanoyl} valine (4-carboxy)phenylmethanamide

- N*-[*N*-(3-hydroxy-3-phenylpropanoyl)-(3*S*, 4*S*)-4-amino-3-hydroxy-6-methylheptanoyl]valine (4-carboxy)phenylmethanamide
- 5 *N*-[*N*-(3, 3, 3-trifluoro-2-methoxy-2-phenylpropanoyl)-(3*S*, 4*S*)-4-amino-3-hydroxy-6-methylheptanoyl]valine (4-carboxy)phenylmethanamide
- N*-{*N*'-[(*R*)-2-hydroxy-4-thiomethylbutanoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-6-methylheptanoyl} valine (4-carboxy)phenylmethanamide
- 10 *N*-[*N*-(2-hydroxy-2-phenylethanoyl)-(3*S*, 4*S*)-4-amino-3-hydroxy-6-methylheptanoyl]valine (4-carboxy)phenylmethanamide
- 15 *N*-[*N*-(2-hydroxy-2-phenylethanoyl)-(3*S*, 4*S*)-4-amino-3-hydroxy-6-methylheptanoyl]valine (4-carboxy)phenylmethanamide
- N*-{*N*'-[(2-hydroxy-2-(naphth-1-yl)ethanoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(4-methylphenyl)pentanoyl} valine (4-carboxy)phenylmethanamide
- 20 *N*-{*N*'-[2-hydroxy-2-(naphth-1-yl)ethanoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(thien-2-yl)pentanoyl} valine (4-carboxy)phenylmethanamide
- N*-{*N*'-[2-hydroxy-2-(naphth-1-yl)ethanoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(thiazol-4-yl)pentanoyl} valine (4-carboxy)phenylmethanamide
- 25 *N*-{*N*'-[3-(*N*'', *N*''-diethylamido)benzoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl} valine *cis,cis*-3,5-dicarboxycyclohexylamide
- 30 *N*-{*N*'-[3-(*N*''-ethyl-*N*''-methylanido)benzoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl} valine
- N*-{*N*'-[3-(*N*''-ethyl-*N*''-methylanido)benzoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl} valine ethylamide
- 35 *N*-{*N*'-[3-(*N*'', *N*''-diethylamido)benzoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl} valine
- N*-{*N*'-[2-hydroxy-2-(naphth-1-yl)ethanoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl} valine *cis,cis*-3,5-dicarboxycyclohexylamide
- 40 *N*-{*N*'-[2-hydroxy-2-(2-phenylphenyl)ethanoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl} valine ethylamide
- 45 *N*-[*N*'-(4-*N*'', *N*''-dimethylamino-5-oxopentanoyl)-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl]valine *cis,cis*-3,5-dicarboxycyclohexylamide
- N*-{*N*'-[3-(*N*''-ethyl-*N*''-methylanido)benzoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl} valine *cis,cis*-3,5-dimethoxycyclohexylamide

- N*-[*N'*-(benzo-1, 4-dioxan-6-oyl)-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl]valine *cis,cis*-3,5-dicarboxycyclohexylamide
- 5 *N*-[*N'*-(3-amidobenzoyl)-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl]valine *cis,cis*-3,5-dicarboxycyclohexylamide
- N*-{*N'*-[3-(*N'*-acetylamino)benzoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl} valine *cis,cis*-3,5-dicarboxycyclohexylamide
- 10 *N*-[*N'*-(3-carbomethoxybenzoyl)-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl]valine *cis,cis*-3,5-dicarboxycyclohexylamide
- N*-{*N'*-[2-hydroxy-2-(2-methoxyphenyl)ethanoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl} valine *cis,cis*-3,5-dicarboxycyclohexylamide
- 15 *N*-{*N'*-[2-hydroxy-2-(4-methoxyphenyl)ethanoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl} valine *cis,cis*-3,5-dicarboxycyclohexylamide
- N*-[*N'*-benzoyl-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl]valine *cis,cis*-3,5-dicarboxycyclohexylamide
- 20 *N*-[*N'*-(naphth-2-oyl)-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl]valine *cis,cis*-3,5-dicarboxycyclohexylamide
- N*-{*N'*-[3-(*N'*-methylpiperazido)benzoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl} valine *cis,cis*-3,5-dicarboxycyclohexylamide
- 25 *N*-{*N'*-[2-hydroxy-2-(4-methoxyphenyl)ethanoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3-trifluoromethylphenyl)pentanoyl} valine *cis,cis*-3,5-dicarboxycyclohexylamide
- N*-{*N'*-[3-(*N''*, *N''*-dipropylamido)phenylmethyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl} valine *cis,cis,cis*-3,4,5-trimethoxycyclohexylamide
- 30 *N*-{*N'*-[5-(*N''*, *N''*-dipropylamido)2,6-dimethylpyrid-3-ylcarbonyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl} valine *cis,cis*-3,5-dicarboxycyclohexylamide
- N*-{*N'*-[3-(*N''*, *N''*-dipropylamido)-2-methoxybenzoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl} valine *cis,cis*-3,5-dicarboxycyclohexylamide
- 35 *N*-{*N'*-[3-(*N''*, *N''*-dipropylamido)-5-methoxybenzoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl} valine *cis,cis*-3,5-dicarboxycyclohexylamide
- 40 *N*-{*N'*-[3-(2-methylpropionyl)-benzoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl} valine *cis,cis*-3,5-dicarboxycyclohexylamide
- N*-{*N'*-[5-(*N''*, *N''*-dipropylamido)-furan-2-ylcarbonyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl} valine *cis,cis*-3,5-dicarboxycyclohexylamide
- 45



*N*-{*N'*-[ 5-(*N''*, *N''*-dipropylamido)-thiophen-2-ylcarbonyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl} valine *cis,cis*-3,5-dicarboxycyclohexylamide

5 *N*-{*N'*-[ 5-(*N''*, *N''*-dipropylamido)-5-methylbenzoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl} valine *cis,cis,cis*-3,4,5-trimethoxycyclohexylamide

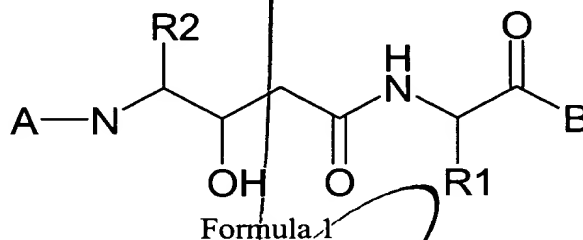
*N*-{*N'*-[3-(*N''*, *N''*-diethylamido)phenylmethyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl} valine *cis,cis*-3,5-dicarboxycyclohexylamide

10 *N*-[*N'*-(3-phenylbenzoyl)-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl]valine *cis,cis*-3,5-dicarboxycyclohexylamide ,and

*N*-[*N'*-2-pyrimidyl-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl]valine *cis,cis*-3,5-dicarboxycyclohexylamide.

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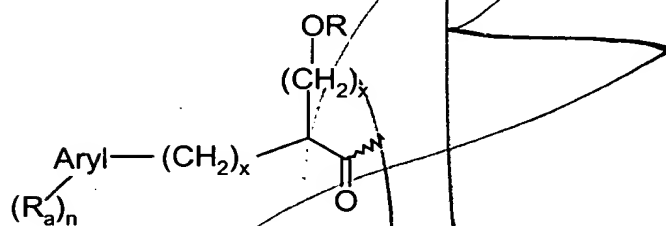
24) A method of slowing or ameliorating the progression of a disease state characterized by deposition of A $\beta$  peptide in a mammal comprising administering to a mammal in need thereof an effective amount of a compound of formula 1



20

wherein:  
A is

25 i)



30

wherein Aryl is mono or bicyclic and has from 5 to 10 ring atoms and may optionally include up to 3 heteroatoms chosen from N, O and S;

each x is independently 0, 1 or 2;

35

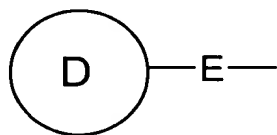
R is H, C<sub>1</sub>-C<sub>6</sub> alkyl, phenyl or benzyl wherein each phenyl ring is optionally substituted with up to two groups independently selected from -OH; -CH<sub>2</sub>OH, -CO<sub>2</sub>H, -CF<sub>3</sub>, Cl, Br, F; and C<sub>1</sub>-C<sub>2</sub> alkyl;

each R<sub>a</sub> is independently selected from the group consisting of H, OH, C<sub>1</sub>-C<sub>3</sub> alkyl; C<sub>1</sub>-C<sub>6</sub> alkylacylamino, C<sub>1</sub>-C<sub>6</sub> alkylacyloxy, C<sub>1</sub>-C<sub>6</sub> alkyloxy, C<sub>1</sub>-C<sub>6</sub> alkylthioxy,

amido (including primary, C<sub>1</sub>-C<sub>6</sub> alkyl and phenyl secondary and tertiary), NH<sub>2</sub>, mono and di(C<sub>1</sub>-C<sub>6</sub> alkyl and phenyl) amino, carbamyl (including C<sub>1</sub>-C<sub>6</sub> alkyl and phenyl amides and esters), carboxyl (including C<sub>1</sub>-C<sub>6</sub> alkyl and phenyl esters), carboxy(C<sub>2</sub>-C<sub>5</sub>)alkyloxy and N-heterocyclacyl;

5 and n is 1 or 2;

ii)



wherein D is chosen from aryl having 5 to 6

10 atoms, optionally including up to 2 heteroatoms selected from the N, O, and S; fused aryl of 8 to 14 atoms optionally including up to 3 heteroatoms selected from the N, O, and S; mono or fused cycloalkyl having 5 to 12 carbon atoms; and mono or fused heterocycloalkyl having 5 to 12 carbon atoms including up to 3 heteroatoms selected from N, O, and S; biaryl, diaryl ether, diarylketone, and phenyl(C<sub>1</sub>-C<sub>8</sub>) alkyloxyaryl;

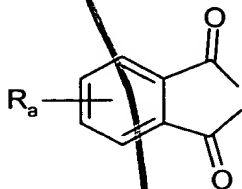
15 and wherein E is a divalent group chosen from carbonyl, sulfonyl, C<sub>1</sub>-C<sub>3</sub> alkylene, -X- (C<sub>1</sub>-C<sub>3</sub>) alkylcarbonyl wherein X is chosen from N, O and S, or E is merely a bond;

and D may optionally be substituted with up to two groups chosen from OH, C<sub>1</sub>-C<sub>3</sub> alkyl; C<sub>1</sub>-C<sub>6</sub> alkylacylamino, C<sub>1</sub>-C<sub>6</sub> alkylacyloxy, C<sub>1</sub>-C<sub>6</sub> alkyloxy, C<sub>1</sub>-C<sub>6</sub> alkylthioxy, amido (including primary, C<sub>1</sub>-C<sub>6</sub> alkyl and phenyl secondary and tertiary), NH<sub>2</sub>, mono and di(C<sub>1</sub>-C<sub>6</sub> alkyl and phenyl) amino, carbamyl (including C<sub>1</sub>-C<sub>6</sub> alkyl and phenyl amides and esters), carboxyl (including C<sub>1</sub>-C<sub>6</sub> alkyl and phenyl esters), carboxy(C<sub>2</sub>-C<sub>5</sub>)alkyloxy, N-heterocyclacyl, C<sub>1</sub>-C<sub>3</sub> alkylsulfonyl, sulfonamide and C<sub>1</sub>-C<sub>3</sub> alkylsulfonamide; --

25 iii) C<sub>1</sub>-C<sub>6</sub> alkanoyl; C<sub>2</sub>-C<sub>6</sub> alkenoyl; and methylthioC<sub>1</sub>-C<sub>5</sub> alkanoyl, any of which may be substituted with up to two groups chosen from OH, C<sub>1</sub>-C<sub>6</sub> alkylacylamino, C<sub>1</sub>-C<sub>6</sub> alkylacyloxy; C<sub>1</sub>-C<sub>6</sub> alkyloxy; C<sub>1</sub>-C<sub>6</sub> alkylthioxy, amido (including primary, C<sub>1</sub>-C<sub>6</sub> alkyl secondary; C<sub>1</sub>-C<sub>6</sub> alkyl and phenyl tertiary, amino, C<sub>1</sub>-C<sub>6</sub> alkyl and phenyl amino, carbamyl (including C<sub>1</sub>-C<sub>6</sub> alkyl and phenyl amides and esters), carboxyl (including C<sub>1</sub>-C<sub>6</sub> alkyl and phenyl esters), carboxy(C<sub>2</sub>-C<sub>5</sub>)alkyloxy and N-heterocyclacyl, C<sub>1</sub>-C<sub>3</sub> alkylsulfonyl, sulfonamide and C<sub>1</sub>-C<sub>3</sub> alkylsulfonamide;

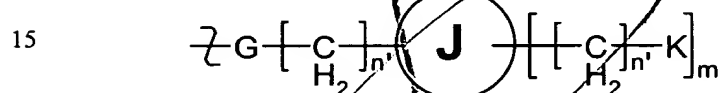
30

and iv) a divalent group of the formula:



10 wherein each carbonyl of the divalent group bonds to the nitrogen to form a five membered ring and R<sub>a</sub> is as defined above;

B is selected from -OH; C<sub>1</sub>-C<sub>6</sub> alkyl or C<sub>1</sub>-C<sub>6</sub> alkyl amino, di(C<sub>1</sub>-C<sub>6</sub> alkyl)amino, C<sub>1</sub>-C<sub>6</sub> alkyloxy, N-heterocyclic and



each n' is independently 0, 1 or 2;

m is 0, 1, 2 or 3;

20 and G is N or O;

J is selected from the group consisting of aryl having a 5 to 6 membered ring optionally including up to 2 heteroatoms selected from the N, O, and S; fused aryl rings of 8 to 14 atoms optionally including up to 3 heteroatoms selected from N, O, and S, mono or fused ring cycloalkyl having 5 to 12 carbon atoms; and mono or fused ring heterocyclic having 5 to 12 carbon atoms including up to 3 heteroatoms chosen from the group consisting of N, O, and S;

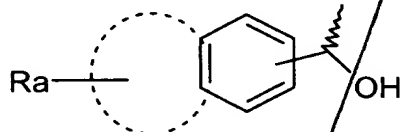
30 each K is chosen from OH, C<sub>1</sub>-C<sub>3</sub> alkyl; C<sub>1</sub>-C<sub>6</sub> alkylacylamino, C<sub>1</sub>-C<sub>6</sub> alkylacyloxy, C<sub>1</sub>-C<sub>6</sub> alkyloxy, C<sub>1</sub>-C<sub>6</sub> alkylthioxy, amido (including primary, C<sub>1</sub>-C<sub>6</sub> alkyl and phenyl secondary and tertiary), NH<sub>2</sub>, mono and di(C<sub>1</sub>-C<sub>6</sub> alkyl and phenyl) amino, carbamyl (including C<sub>1</sub>-C<sub>6</sub> alkyl and phenyl amides and esters), carboxyl (including C<sub>1</sub>-C<sub>6</sub> alkyl and phenyl esters) and carboxy(C<sub>2</sub>-C<sub>5</sub>)alkyloxy;

R<sub>1</sub> is straight or branched chain C<sub>1</sub>-C<sub>5</sub> alkanyl or C<sub>2</sub>-C<sub>5</sub> alkenyl;

35 R<sub>2</sub> is C<sub>1-5</sub> straight or branched chain alkanyl or alkenyl; methylthiomethyl; aryl or arylalkyl or heteroaryl or heteroarylalkyl wherein any of the above are optionally substituted with up to 2 of C<sub>1-3</sub> alkyl, trifluoromethyl or halogen,

and pharmaceutically acceptable salts and esters thereof.

25) The method claim 24 wherein A is:

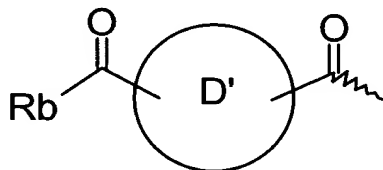


wherein the dotted line indicates an optional aryl ring fused to the phenyl ring.

26) The method of claim 25 wherein the A is selected from 2-hydroxy-(2-phenyl)ethanoyl, 2-hydroxy-(2-naphth-1-yl)ethanoyl, and 2-hydroxy-(2-naphth-12-yl)ethanoyl.

27) The method of claim 24 wherein A is selected from biphenyl, 2-phenyl- $\alpha$ -hydroxytolyl, diphenyl ether and diphenyl ketone.

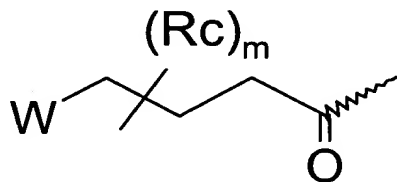
28) The method of claim 24 wherein A is



wherein the ring D' is a 5 or 6 membered monocyclic aryl or heteroaryl ring including up to 3 atoms selected from N, O and S; and Rb is  $\text{-NH}_2$ , mono and di( $\text{C}_1\text{-C}_6$  alkyl) amino,  $\text{C}_1\text{-C}_6$  alkoxy, N-heterocyclic and  $\text{C}_1\text{-C}_6$  alkyl.

29) The method of claim 28 wherein the ring D' is chosen from the group consisting of benzene, pyridine, furan, thiophene, thiazole, thiadiazole, oxazole, oxadiazole and 1,2,4-triazole and Rb is di( $\text{C}_2\text{-C}_4$ )alkylamine.

30) The method of claim 24 wherein A is



wherein W is selected from  $\text{C}_1\text{-C}_3$  alkylthio,  $\text{C}_1\text{-C}_3$  alkylsulfonyl, primary amido, secondary and tertiary  $\text{C}_1\text{-C}_3$  alkyl amido, N-heterocyclacyl, primary sulfonamide, secondary and tertiary  $\text{C}_1\text{-C}_3$  alkyl sulfonamide, and carboxylic acid and  $\text{C}_1\text{-C}_3$  alkyl

esters, R<sub>c</sub> may optionally substitute the alkylene chain and is selected from -OH, C<sub>1</sub>-C<sub>3</sub> alkyl, Cl and F, and m is 0, 1, 2 or 3

31) The method of claim 1 wherein R<sub>1</sub> is selected from ethyl and 2-propyl.

32) The method of claim 24 wherein R<sub>2</sub> is selected from 2-thienylmethyl, 3-trifluoromethylphenylmethyl, 4-thiazolylmethyl, 3-chlorophenylmethyl, 3,5-difluorophenylmethyl, 4-methylphenylmethyl and 2-methylprop-1-yl.

33) The method of claim 24 wherein R<sub>1</sub> is 2-propyl and R<sub>2</sub> is 3,5-difluorophenylmethyl.

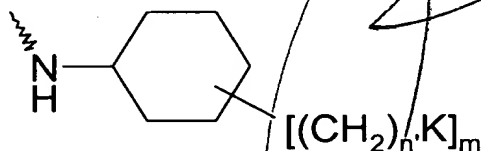
34) The method of claim 26 wherein R<sub>1</sub> is 2-propyl and R<sub>2</sub> is 3,5-difluorophenylmethyl.

35) The method of claim 28 wherein R<sub>1</sub> is 2-propyl and R<sub>2</sub> is 3,5-difluorophenylmethyl.

36) The method of claim 30 wherein R<sub>1</sub> is 2-propyl and R<sub>2</sub> is 3,5-difluorophenylmethyl.

37) The method of claim 24 wherein B is -OH, C<sub>1</sub>-C<sub>6</sub> alkoxy, mono and di(C<sub>1</sub>-C<sub>6</sub>) alkylamino, amino C<sub>1</sub>-C<sub>4</sub> alkyl-p-benzoic acid and C<sub>1</sub>-C<sub>6</sub> alkyl and phenyl esters thereof and N-heterocyclic.

38) The method of claim 1 wherein B is



wherein K, n' and m are as defined in claim 1.

39) The method of claim 38 wherein B is selected from 3,5-dicarboxycyclohexylamine, 3,4- dicarboxycyclohexylamine, 3,5- dimethoxycyclohexylamine, 3,5-dihydroxymethylcyclohexylamine and 3,4,5-trimethoxycyclohexylamine.

40) The method of claim 24 wherein A is selected according to claim 25 and B is selected according to claim 37.

41) The method of claim 24 wherein A is selected according to claim 25 and B is selected according to claim 38.

- 42) The method of claim 24 wherein A is selected according to claim 28 and B is selected according to claim 37.
- 5 43) The method of claim 24 wherein A is selected according to claim 28 and B is selected according to claim 38.
- 44) The method of claim 24 wherein A is selected according to claim 30 and B is selected according to claim 37.
- 10 45) The method of claim 24 wherein A is selected according to claim 30 and B is selected according to claim 38.
- 46) A method of slowing or ameliorating the progression of a disease state characterized by deposition of A $\beta$  peptide in a mammal comprising administering to a mammal in need thereof an effective amount of a compound selected from the group consisting of:
- 15 *N*-{*N'*-[2-hydroxy-2-(naphth-1-yl)ethanoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-6-methylheptanoyl} valine (4-carboxy)phenylmethanamide
- 20 *N*-{*N'*-[2-hydroxy-2-(naphth-1-yl)ethanoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-6-methylheptanoyl} valine 2-[(4-carboxy)phenyl]ethylamide
- 25 *N*-{*N'*-[2-hydroxy-2-(naphth-1-yl)ethanoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-6-methylheptanoyl} valine 3-carboxypropylamide
- N*-{*N'*-[2-hydroxy-2-(naphth-1-yl)ethanoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-6-methylheptanoyl} valine 4-carboxynaphth-1-ylmethanamide
- 30 *N*-{*N'*-[2-hydroxy-2-(naphth-1-yl)ethanoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-6-methylheptanoyl} valine *cis,cis*-3,5-dicarboxycyclohexylamide
- N*-{*N'*-[2-hydroxy-2-(naphth-1-yl)ethanoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-6-methylheptanoyl} valine 4-carboxycyclohexylamide
- 35 *N*-{*N'*-[2-hydroxy-2-(naphth-1-yl)ethanoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-6-methylheptanoyl} valine
- 40 *N*-{*N'*-[2-benzyloxy-2-(naphth-1-yl)ethanoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-6-methylheptanoyl} valine (4-carboxy)phenylmethanamide
- N*-[*N'*-(3-hydroxy-2-phenylpropanoyl)-(3*S*, 4*S*)-4-amino-3-hydroxy-6-methylheptanoyl]valine (4-carboxy)phenylmethanamide

- N*-{*N'*-[2-hydroxy-2-(2-bromophenyl)ethanoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-6-methylheptanoyl} valine (4-carboxy)phenylmethanamide
- 5 *N*-{*N'*-[(*S*)-2-hydroxy-3-phenylpropanoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-6-methylheptanoyl} valine (4-carboxy)phenylmethanamide
- N*-{*N'*-[2-hydroxy-2-(3-phenoxyphenyl)ethanoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-6-methylheptanoyl} valine (4-carboxy)phenylmethanamide
- 10 *N*-{*N'*-[(*R*)-2-hydroxy-3-phenylpropanoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-6-methylheptanoyl} valine (4-carboxy)phenylmethanamide
- N*-[*N'*-(3-hydroxy-3-phenylpropanoyl)-(3*S*, 4*S*)-4-amino-3-hydroxy-6-methylheptanoyl]valine (4-carboxy)phenylmethanamide
- 15 *N*-[*N'*-(3, 3, 3-trifluoro-2-methoxy-2-phenylpropanoyl)-(3*S*, 4*S*)-4-amino-3-hydroxy-6-methylheptanoyl]valine (4-carboxy)phenylmethanamide
- 20 *N*-{*N'*-[(*R*)-2-hydroxy-4-thiomethylbutanoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-6-methylheptanoyl} valine (4-carboxy)phenylmethanamide
- N*-[*N'*-(2-hydroxy-2-phenylethanoyl)-(3*S*, 4*S*)-4-amino-3-hydroxy-6-methylheptanoyl]valine (4-carboxy)phenylmethanamide
- 25 *N*-[*N'*-(2-hydroxy-2-phenylethanoyl)-(3*S*, 4*S*)-4-amino-3-hydroxy-6-methylheptanoyl]valine (4-carboxy)phenylmethanamide
- N*-{*N'*-[(2-hydroxy-2-(naphth-1-yl)ethanoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(4-methylphenyl)pentanoyl} valine (4-carboxy)phenylmethanamide
- 30 *N*-{*N'*-[2-hydroxy-2-(naphth-1-yl)ethanoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(thien-2-yl)pentanoyl} valine (4-carboxy)phenylmethanamide
- 35 *N*-{*N'*-[2-hydroxy-2-(naphth-1-yl)ethanoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(thiazol-4-yl)pentanoyl} valine (4-carboxy)phenylmethanamide
- N*-{*N'*-[3-(*N'*, *N''*-diethylamido)benzoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl} valine *cis*, *cis*-3,5-dicarboxycyclohexylamide
- 40 *N*-{*N'*-[3-(*N'*-ethyl-*N''*-methylanido)benzoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl} valine
- N*-{*N'*-[3-(*N'*-ethyl-*N''*-methylanido)benzoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl} valine ethylamide
- 45 *N*-{*N'*-[3-(*N'*, *N''*-diethylamido)benzoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl} valine

- N*-{*N'*-[2-hydroxy-2-(naphth-1-yl)ethanoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl} valine *cis,cis*-3,5-dicarboxycyclohexylamide
- 5 *N*-{*N'*-[2-hydroxy-2-(2-phenylphenyl)ethanoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl} valine ethylamide
- N*-[*N'*-(4-*N''*, *N''*-dimethylamino-5-oxopentanoyl)-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl] valine *cis,cis*-3,5-dicarboxycyclohexylamide
- 10 *N*-{*N'*-[3-(*N''*-ethyl-*N''*-methyamido)benzoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl} valine *cis,cis*-3,5-dimethoxycyclohexylamide
- N*-[*N'*-(benzo-1, 4-dioxan-6-oyl)-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl] valine *cis,cis*-3,5-dicarboxycyclohexylamide
- 15 *N*-[*N'*-(3-amidobenzoyl)-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl] valine *cis,cis*-3,5-dicarboxycyclohexylamide
- N*-{*N'*-[3-(*N''*-acetylamino)benzoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl} valine *cis,cis*-3,5-dicarboxycyclohexylamide
- 20 *N*-[*N'*-(3-carbomethoxybenzoyl)-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl] valine *cis,cis*-3,5-dicarboxycyclohexylamide
- 25 *N*-{*N'*-[2-hydroxy-2-(2-methoxyphenyl)ethanoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl} valine *cis,cis*-3,5-dicarboxycyclohexylamide
- N*-{*N'*-[2-hydroxy-2-(4-methoxyphenyl)ethanoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl} valine *cis,cis*-3,5-dicarboxycyclohexylamide
- 30 *N*-[*N'*-benzoyl-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl] valine *cis,cis*-3,5-dicarboxycyclohexylamide
- N*-[*N'*-(naphth-2-oyl)-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl] valine *cis,cis*-3,5-dicarboxycyclohexylamide
- 35 *N*-{*N'*-[3-(*N''*-methylpiperazido)benzoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl} valine *cis,cis*-3,5-dicarboxycyclohexylamide
- N*-{*N'*-[2-hydroxy-2-(4-methoxyphenyl)ethanoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3-trifluoromethylphenyl)pentanoyl} valine *cis,cis*-3,5-dicarboxycyclohexylamide
- 40 *N*-{*N'*-[3-(*N''*, *N''*-dipropylamido)phenylmethyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl} valine *cis,cis,cis*-3,4,5-trimethoxycyclohexylamide
- N*-{*N'*-[5-(*N''*, *N''*-dipropylamido)2,6-dimethylpyrid-3-ylcarbonyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl} valine *cis,cis*-3,5-dicarboxycyclohexylamide
- 45



*N*-{*N'*-[3-(*N''*, *N''*-dipropylamido)-2-methoxybenzoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl} valine *cis,cis*-3,5-dicarboxycyclohexylamide

5 *N*-{*N'*-[3-(*N''*, *N''*-dipropylamido)-5-methoxybenzoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl} valine *cis,cis*-3,5-dicarboxycyclohexylamide

*N*-{*N'*-[3-(2-methylpropionyl)-benzoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl} valine *cis,cis*-3,5-dicarboxycyclohexylamide

10 *N*-{*N'*-[5-(*N''*, *N''*-dipropylamido)-furan-2-ylcarbonyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl} valine *cis,cis*-3,5-dicarboxycyclohexylamide

*N*-{*N'*-[5-(*N''*, *N''*-dipropylamido)-thiophen-2-ylcarbonyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl} valine *cis,cis*-3,5-dicarboxycyclohexylamide

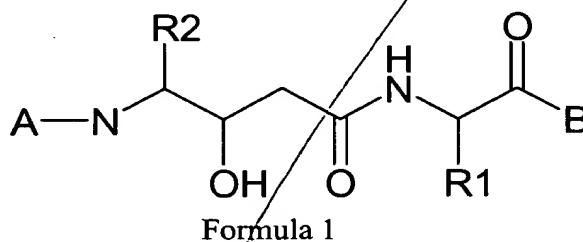
15 *N*-{*N'*-[5-(*N''*, *N''*-dipropylamido)-5-methylbenzoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl} valine *cis,cis,cis*-3,4,5-trimethoxycyclohexylamide

20 *N*-{*N'*-[3-(*N''*, *N''*-diethylamido)phenylmethyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl} valine *cis,cis*-3,5-dicarboxycyclohexylamide

*N*-[*N'*-(3-phenylbenzoyl)-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl]valine *cis,cis*-3,5-dicarboxycyclohexylamide, and

25 *N*-[*N'*-2-pyrimidyl-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl]valine *cis,cis*-3,5-dicarboxycyclohexylamide.

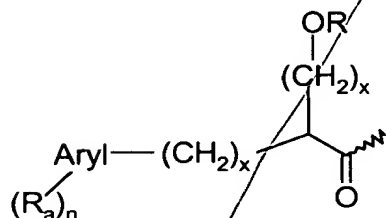
47) A pharmaceutical composition comprising a compound of formula 1



wherein:

A is

35 i)



wherein Aryl is mono or bicyclic and has from 5 to 10 ring atoms and may optionally include up to 3 heteroatoms chosen from N, O and S;

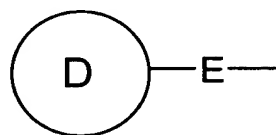
each x is independently 0, 1 or 2;

R is H, C<sub>1</sub>-C<sub>6</sub> alkyl, phenyl or benzyl wherein each phenyl ring is optionally substituted with up to two groups independently selected from -OH; -CH<sub>2</sub>OH, -CO<sub>2</sub>H, -CF<sub>3</sub>, Cl, Br, F; and C<sub>1</sub>-C<sub>2</sub> alkyl;

5 each R<sub>a</sub> is independently selected from the group consisting of H, OH, C<sub>1</sub>-C<sub>3</sub> alkyl; C<sub>1</sub>-C<sub>6</sub> alkylacylamino, C<sub>1</sub>-C<sub>6</sub> alkylacyloxy, C<sub>1</sub>-C<sub>6</sub> alkyloxy, C<sub>1</sub>-C<sub>6</sub> alkylthioxy, amido (including primary, C<sub>1</sub>-C<sub>6</sub> alkyl and phenyl secondary and tertiary), NH<sub>2</sub>, mono and di(C<sub>1</sub>-C<sub>6</sub> alkyl and phenyl) amino, carbamyl (including C<sub>1</sub>-C<sub>6</sub> alkyl and phenyl amides and esters), carboxyl (including C<sub>1</sub>-C<sub>6</sub> alkyl and phenyl esters), carboxy(C<sub>2</sub>-C<sub>5</sub>)alkyloxy and N-heterocyclacyl;

10 and n is 1 or 2;

ii)



wherein D is chosen from aryl having 5 to 6 atoms, optionally including up to 2 heteroatoms selected from the N, O, and S; fused aryl of 8 to 14 atoms optionally including up to 3 heteroatoms selected from the N, O, and S; mono or fused cycloalkyl having 5 to 12 carbon atoms; and mono or fused heterocycloalkyl having 5 to 12 carbon atoms including up to 3 heteroatoms selected from N, O, and S; biaryl, diaryl ether; diarylketone, and phenyl(C<sub>1</sub>-C<sub>8</sub>) alkyloxyaryl;

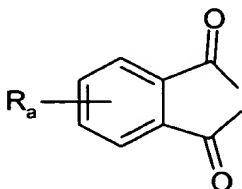
20 and wherein E is a divalent group chosen from carbonyl, sulfonyl, C<sub>1</sub>-C<sub>3</sub> alkylene, -X- (C<sub>1</sub>-C<sub>3</sub>) alkylcarbonyl wherein X is chosen from N, O and S, or E is merely a bond;

and D may optionally be substituted with up to two groups chosen from OH, C<sub>1</sub>-C<sub>3</sub> alkyl; C<sub>1</sub>-C<sub>6</sub> alkylacylamino, C<sub>1</sub>-C<sub>6</sub> alkylacyloxy, C<sub>1</sub>-C<sub>6</sub> alkyloxy, C<sub>1</sub>-C<sub>6</sub> alkylthioxy, amido (including primary, C<sub>1</sub>-C<sub>6</sub> alkyl and phenyl secondary and tertiary), NH<sub>2</sub>, mono and di(C<sub>1</sub>-C<sub>6</sub> alkyl and phenyl) amino, carbamyl (including C<sub>1</sub>-C<sub>6</sub> alkyl and phenyl amides and esters), carboxyl (including C<sub>1</sub>-C<sub>6</sub> alkyl and phenyl esters), carboxy(C<sub>2</sub>-C<sub>5</sub>)alkyloxy, N-heterocyclacyl, C<sub>1</sub>-C<sub>3</sub> alkylsulfonyl, sulfonamide and C<sub>1</sub>-C<sub>3</sub> alkylsulfonamide;

30 iii) C<sub>1</sub>-C<sub>6</sub> alkanoyl; C<sub>2</sub>-C<sub>6</sub> alkenoyl; and methylthioC<sub>1</sub>-C<sub>5</sub> alkanoyl, any of which may be substituted with up to two groups chosen from OH, C<sub>1</sub>-C<sub>6</sub> alkylacylamino, C<sub>1</sub>-C<sub>6</sub> alkylacyloxy; C<sub>1</sub>-C<sub>6</sub> alkyloxy; C<sub>1</sub>-C<sub>6</sub> alkylthioxy, amido (including primary, C<sub>1</sub>-C<sub>6</sub> alkyl

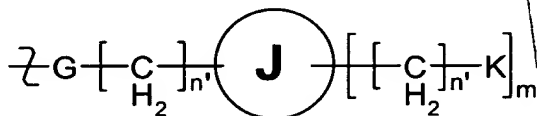
secondary; C<sub>1</sub>-C<sub>6</sub> alkyl and phenyl tertiary, amino, C<sub>1</sub>-C<sub>6</sub> alkyl and phenyl amino, carbamyl (including C<sub>1</sub>-C<sub>6</sub> alkyl and phenyl amides and esters), carboxyl (including C<sub>1</sub>-C<sub>6</sub> alkyl and phenyl esters), carboxy(C<sub>2</sub>-C<sub>5</sub>)alkyloxy and N-heterocyclacyl, C<sub>1</sub>-C<sub>3</sub> alkylsulfonyl, sulfonamide and C<sub>1</sub>-C<sub>3</sub> alkylsulfonamide;

and iv) a divalent group of the formula:



wherein each carbonyl of the divalent group bonds to the nitrogen to form a five membered ring and R<sub>a</sub> is as defined above;

B is selected from -OH; C<sub>1</sub>-C<sub>6</sub> alkyl or C<sub>1</sub>-C<sub>6</sub> alkyl amino, di(C<sub>1</sub>-C<sub>6</sub> alkyl)amino, C<sub>1</sub>-C<sub>6</sub> alkyloxy, N-heterocyclic and



each n' is independently 0, 1 or 2;

m is 0, 1, 2 or 3;

and G is N or O;

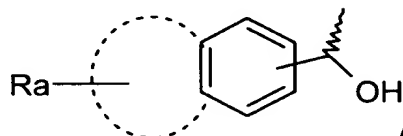
J is selected from the group consisting of aryl having a 5 to 6 membered ring optionally including up to 2 heteroatoms selected from the N, O, and S; fused aryl rings of 8 to 14 atoms optionally including up to 3 heteroatoms selected from N, O, and S, mono or fused ring cycloalkyl having 5 to 12 carbon atoms; and mono or fused ring heterocyclic having 5 to 12 carbon atoms including up to 3 heteroatoms chosen from the group consisting of N, O, and S;

each K is chosen from OH, C<sub>1</sub>-C<sub>3</sub> alkyl; C<sub>1</sub>-C<sub>6</sub> alkylacylamino, C<sub>1</sub>-C<sub>6</sub> alkylacyloxy, C<sub>1</sub>-C<sub>6</sub> alkyloxy, C<sub>1</sub>-C<sub>6</sub> alkylthioxy, amido (including primary, C<sub>1</sub>-C<sub>6</sub> alkyl and phenyl secondary and tertiary), NH<sub>2</sub>, mono and di(C<sub>1</sub>-C<sub>6</sub> alkyl and phenyl) amino, carbamyl (including C<sub>1</sub>-C<sub>6</sub> alkyl and phenyl amides and esters), carboxyl (including C<sub>1</sub>-C<sub>6</sub> alkyl and phenyl esters) and carboxy(C<sub>2</sub>-C<sub>5</sub>)alkyloxy;

R1 is straight or branched chain C<sub>1</sub>-C<sub>5</sub> alkanyl or C<sub>2</sub>-C<sub>5</sub> alkenyl;

R2 is C<sub>1-5</sub> straight or branched chain alkanyl or alkenyl; methylthiomethyl; aryl or arylalkyl or heteroaryl or heteroarylalkyl wherein any of the above are optionally substituted with up to 2 of C<sub>1-3</sub> alkyl, trifluoromethyl or halogen, and and pharmaceutically acceptable salts and esters thereof and a pharmaceutically acceptable diluent.

48) The composition claim 47 wherein A is:

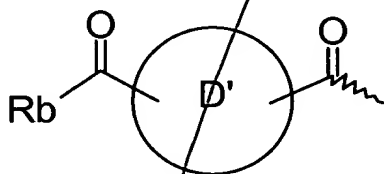


wherein the dotted line indicates an optional aryl ring fusion

49) The composition of claim 48 wherein the A is selected from phenyl)ethanoyl, 2-hydroxy-(2-naphth-1-yl)ethanoyl, aryl)ethanoyl.

50) The composition of claim 47 wherein A is selected from hydroxytolyl, diphenyl ether and diphenyl ketone.

51) The composition of claim 47 wherein A is

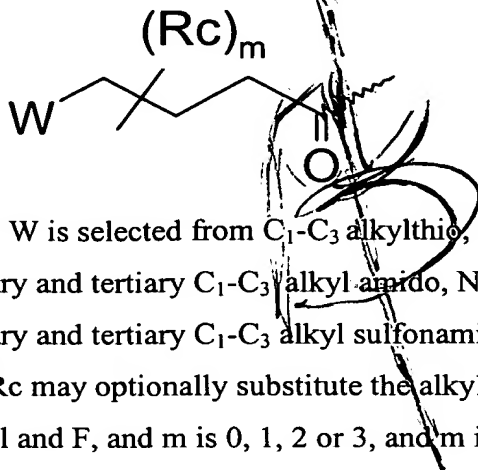


wherein the ring D' is a 5 or 6 membered monocyclic aryl or heteroaryl ring including up to 3 atoms selected from N, O and S, and Rb is -NH<sub>2</sub>, mono and di(C<sub>1</sub>-C<sub>6</sub> alkyl) amino, C<sub>1</sub>-C<sub>6</sub> alkoxy, N-heterocyclic and C<sub>1</sub>-C<sub>6</sub> alkyl.

52) The composition of claim 51 wherein the ring D' is chosen from the group consisting of benzene, pyridine, furan, thiophene, thiazole, thiadiazole, oxazole, oxadiazole and 1,2,4-triazole and Rb is di(C<sub>2</sub>-C<sub>4</sub>)alkylamine.

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53) The composition of claim 47 wherein A is



wherein W is selected from C<sub>1</sub>-C<sub>3</sub> alkylthio, C<sub>1</sub>-C<sub>3</sub> alkylsulfonyl, primary amido, secondary and tertiary C<sub>1</sub>-C<sub>3</sub> alkyl amido, N-heterocyclacyl, primary sulfonamide, secondary and tertiary C<sub>1</sub>-C<sub>3</sub> alkyl sulfonamide, and carboxylic acid and C<sub>1</sub>-C<sub>3</sub> alkyl esters, Rc may optionally substitute the alkylene chain and is selected from -OH, C<sub>1</sub>-C<sub>3</sub> alkyl, Cl and F, and m is 0, 1, 2 or 3, and m is 0, 1, 2 or 3.

54) The composition of claim 47 wherein R<sub>1</sub> is selected from ethyl and 2-propyl.

55) The composition of claim 47 wherein R<sub>2</sub> is selected from 2-thienylmethyl, 3-trifluoromethylphenylmethyl, 4-thiazolylmethyl, 3-chlorophenylmethyl, 3,5-difluorophenylmethyl, 4-methylphenylmethyl and 2-methylprop-1-yl.

56) The composition of claim 47 wherein R<sub>1</sub> is 2-propyl and R<sub>2</sub> is 3,5-difluorophenylmethyl.

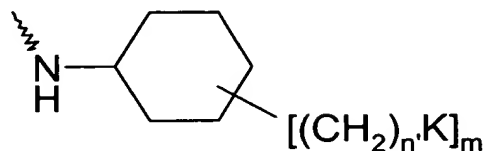
57) The composition of claim 49 wherein R<sub>1</sub> is 2-propyl and R<sub>2</sub> is 3,5-difluorophenylmethyl.

58) The composition of claim 51 wherein R<sub>1</sub> is 2-propyl and R<sub>2</sub> is 3,5-difluorophenylmethyl.

59) The composition of claim 53 wherein R<sub>1</sub> is 2-propyl and R<sub>2</sub> is 3,5-difluorophenylmethyl.

60) The composition of claim 47 wherein B is -OH, C<sub>1</sub>-C<sub>6</sub> alkoxy, mono and di(C<sub>1</sub>-C<sub>6</sub>) alkylamino, amino C<sub>1</sub>-C<sub>4</sub> alkyl-p-benzoic acid and C<sub>1</sub>-C<sub>6</sub> alkyl and phenyl esters thereof and N-heterocyclic.

61) The composition of claim 47 wherein Bis



wherein K, n' and m are as defined in claim 1.

62) The composition of claim 61 wherein B is selected from 3,5-dicarboxycyclohexylamine, 3,4- dicarboxycyclohexylamine, 3,5- dimethoxycyclohexylamine, 3,5-dihydroxymethylcyclohexylamine and 3,4,5-trimethoxycyclohexylamine.

63) The composition of claim 47 wherein A is selected according to claim 48 and B is selected according to claim 60.

64) The composition of claim 47 wherein A is selected according to claim 48 and B is selected according to claim 61.

65) The composition of claim 47 wherein A is selected according to claim 51 and B is selected according to claim 60.

66) The composition of claim 47 wherein A is selected according to claim 51 and B is selected according to claim 61.

67) The composition of claim 47 wherein A is selected according to claim 53 and B is selected according to claim 60.

68) The composition of claim 47 wherein A is selected according to claim 53 and B is selected according to claim 61.

69) A pharmaceutical composition comprising a compound selected from the group consisting of:

*N*-{*N'*-[2-hydroxy-2-(naphth-1-yl)ethanoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-6-methylheptanoyl} valine (4-carboxy)phenylmethanamide

*N*-{*N'*-[2-hydroxy-2-(naphth-1-yl)ethanoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-6-methylheptanoyl} valine 2-[(4-carboxy)phenyl]ethanamide

- N*-{*N'*-[2-hydroxy-2-(naphth-1-yl)ethanoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-6-methylheptanoyl} valine 3-carboxypropylamide
- 5 *N*-{*N'*-[2-hydroxy-2-(naphth-1-yl)ethanoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-6-methylheptanoyl} valine 4-carboxynaphth-1-ylmethanamide
- N*-{*N'*-[2-hydroxy-2-(naphth-1-yl)ethanoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-6-methylheptanoyl} valine *cis,cis*-3,5-dicarboxycyclohexylamide
- 10 *N*-{*N'*-[2-hydroxy-2-(naphth-1-yl)ethanoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-6-methylheptanoyl} valine 4-carboxycyclohexylamide
- N*-{*N'*-[2-hydroxy-2-(naphth-1-yl)ethanoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-6-methylheptanoyl} valine
- 15 *N*-{*N'*-[2-benzyloxy-2-(naphth-1-yl)ethanoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-6-methylheptanoyl} valine (4-carboxy)phenylmethanamide
- N*-[*N'*-(3-hydroxy-2-phenylpropanoyl)-(3*S*, 4*S*)-4-amino-3-hydroxy-6-methylheptanoyl] valine (4-carboxy)phenylmethanamide
- 20 *N*-{*N'*-[2-hydroxy-2-(2-bromophenyl)ethanoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-6-methylheptanoyl} valine (4-carboxy)phenylmethanamide
- N*-{*N'*-[(*S*)-2-hydroxy-3-phenylpropanoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-6-methylheptanoyl} valine (4-carboxy)phenylmethanamide
- 25 *N*-{*N'*-[2-hydroxy-2-(3-phenoxyphenyl)ethanoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-6-methylheptanoyl} valine (4-carboxy)phenylmethanamide
- 30 *N*-{*N'*-[(*R*)-2-hydroxy-3-phenylpropanoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-6-methylheptanoyl} valine (4-carboxy)phenylmethanamide
- N*-[*N'*-(3-hydroxy-3-phenylpropanoyl)-(3*S*, 4*S*)-4-amino-3-hydroxy-6-methylheptanoyl] valine (4-carboxy)phenylmethanamide
- 35 *N*-[*N'*-(3, 3, 3-trifluoro-2-methoxy-2-phenylpropanoyl)-(3*S*, 4*S*)-4-amino-3-hydroxy-6-methylheptanoyl] valine (4-carboxy)phenylmethanamide
- N*-{*N'*-[(*R*)-2-hydroxy-4-thiomethylbutanoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-6-methylheptanoyl} valine (4-carboxy)phenylmethanamide
- 40 *N*-[*N'*-(2-hydroxy-2-phenylethanoyl)-(3*S*, 4*S*)-4-amino-3-hydroxy-6-methylheptanoyl] valine (4-carboxy)phenylmethanamide
- 45 *N*-[*N'*-(2-hydroxy-2-phenylethanoyl)-(3*S*, 4*S*)-4-amino-3-hydroxy-6-methylheptanoyl] valine (4-carboxy)phenylmethanamide

- N*-{*N'*-(2-hydroxy-2-(naphth-1-yl)ethanoyl)-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(4-methylphenyl)pentanoyl} valine (4-carboxy)phenylmethanamide
- 5 *N*-{*N'*-[2-hydroxy-2-(naphth-1-yl)ethanoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(thien-2-yl)pentanoyl} valine (4-carboxy)phenylmethanamide
- N*-{*N'*-[2-hydroxy-2-(naphth-1-yl)ethanoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(thiazol-4-yl)pentanoyl} valine (4-carboxy)phenylmethanamide
- 10 *N*-{*N'*-[3-(*N''*, *N''*-diethylamido)benzoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl} valine *cis,cis*-3,5-dicarboxycyclohexanamide
- N*-{*N'*-[3-(*N''*-ethyl-*N''*-methanamido)benzoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl} valine
- 15 *N*-{*N'*-[3-(*N''*-ethyl-*N''*-methanamido)benzoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl} valine ethanamide
- N*-{*N'*-[3-(*N''*, *N''*-diethylamido)benzoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl} valine
- 20 *N*-{*N'*-[2-hydroxy-2-(naphth-1-yl)ethanoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl} valine *cis,cis*-3,5-dicarboxycyclohexanamide
- N*-{*N'*-[2-hydroxy-2-(2-phenylphenyl)ethanoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl} valine ethanamide
- 25 *N*-[*N'*-(4-*N''*, *N''*-dimethanamino-5-oxopentanoyl)-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl] valine *cis,cis*-3,5-dicarboxycyclohexanamide
- 30 *N*-{*N'*-[3-(*N''*-ethyl-*N''*-methanamido)benzoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl} valine *cis,cis*-3,5-dimethoxycyclohexanamide
- N*-[*N'*-(benzo-1, 4-dioxan-6-oyl)-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl] valine *cis,cis*-3,5-dicarboxycyclohexanamide
- 35 *N*-[*N'*-(3-amidobenzoyl)-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl] valine *cis,cis*-3,5-dicarboxycyclohexanamide
- N*-{*N'*-[3-(*N''*-acetanilamido)benzoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl} valine *cis,cis*-3,5-dicarboxycyclohexanamide
- 40 *N*-[*N'*-(3-carbomethoxybenzoyl)-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl] valine *cis,cis*-3,5-dicarboxycyclohexanamide
- 45 *N*-{*N'*-[2-hydroxy-2-(2-methoxyphenyl)ethanoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl} valine *cis,cis*-3,5-dicarboxycyclohexanamide



*N*-{*N'*-[2-hydroxy-2-(4-methoxyphenyl)ethanoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl} valine *cis,cis*-3,5-dicarboxycyclohexylamide

5 *N*-[*N'*-benzoyl-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl]valine *cis,cis*-3,5-dicarboxycyclohexylamide

*N*-[*N'*-(naphth-2-oyl)-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl]valine *cis,cis*-3,5-dicarboxycyclohexylamide

10 *N*-{*N'*-[3-(*N'*-methylpiperazido)benzoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl} valine *cis,cis*-3,5-dicarboxycyclohexylamide

*N*-{*N'*-[2-hydroxy-2-(4-methoxyphenyl)ethanoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3-trifluoromethylphenyl)pentanoyl} valine *cis,cis*-3,5-dicarboxycyclohexylamide

15 *N*-{*N'*-[3-(*N''*, *N''*-dipropylamido)phenylmethyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl} valine *cis,cis,cis*-3,4,5-trimethoxycyclohexylamide

*N*-{*N'*-[5-(*N''*, *N''*-dipropylamido)2,6-dimethylpyrid-3-ylcarbonyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl} valine *cis,cis*-3,5-dicarboxycyclohexylamide

20 *N*-{*N'*-[3-(*N''*, *N''*-dipropylamido)-2-methoxybenzoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl} valine *cis,cis*-3,5-dicarboxycyclohexylamide

*N*-{*N'*-[3-(*N''*, *N''*-dipropylamido)-5-methoxybenzoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl} valine *cis,cis*-3,5-dicarboxycyclohexylamide

25 *N*-{*N'*-[3-(2-methylpropionyl)-benzoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl} valine *cis,cis*-3,5-dicarboxycyclohexylamide

30 *N*-{*N'*-[5-(*N''*, *N''*-dipropylamido)-furan-2-ylcarbonyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl} valine *cis,cis*-3,5-dicarboxycyclohexylamide

*N*-{*N'*-[5-(*N''*, *N''*-dipropylamido)-thiophen-2-ylcarbonyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl} valine *cis,cis*-3,5-dicarboxycyclohexylamide

35 *N*-{*N'*-[5-(*N''*, *N''*-dipropylamido)-5-methylbenzoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl} valine *cis,cis,cis*-3,4,5-trimethoxycyclohexylamide

*N*-{*N'*-[3-(*N''*, *N''*-diethylamido)phenylmethyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl} valine *cis,cis*-3,5-dicarboxycyclohexylamide

40 *N*-[*N'*-(3-phenylbenzoyl)-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl]valine *cis,cis*-3,5-dicarboxycyclohexylamide, and

45 *N*-[*N'*-2-pyrimidyl-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl]valine *cis,cis*-3,5-dicarboxycyclohexylamide,

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